Biomarker positive and negative subjects in the ADNI cohort: clinical characterization.

BACKGROUND: The Alzheimer's Disease Neuroimaging Initiative (ADNI) was created to develop standards for brain imaging and biomarkers for diagnosis and treatment trials. Using the ADNI dataset, experts have found that low cerebrospinal fluid amyloid-β1-42 (CSF Aβ1-42) concentration and high total-tau/Aβ1-42 ratio are highly predictive of progression in amnestic mild cognitive impairment (aMCI), and recommended these biomarkers to support the diagnosis of prodromal Alzheimer's disease and select patients for clinical trials. However, biomarker selection criteria may introduce systematic bias that undermines their utility.

METHODS: We tested for systematic biases among individuals undergoing lumbar puncture in the ADNI dataset who fulfilled the following entry criteria: (1) aMCI with CSF Aβ1-42 ≤ 192 pG/mL, compared to aMCI with Aβ1-42 > 192 pG/mL, and (2) aMCI with total-tau/Aβ1-42 > 0.39, compared to aMCI with total-tau/Aβ1-42 ≤ 0.39, as well as comparisons between participants with aMCI with and without lumbar puncture.

FINDINGS: Individuals with low CSF Aβ1-42 scored significantly poorer than individuals with high Aβ1-42 on several baseline measures of disease severity, including Logical Memory II (3.24 vs 4.73; p < 0.001), Functional Activities Questionnaire (4.30 vs 2.37; p < 0.001), and Alzheimer's Disease Assessment Scale-cognitive (12.23 vs 10.09; p=0.002). Similar results were found using high total-tau/Aβ1-42. No differences
were found for individuals with and without lumbar puncture except for marital status.

**INTERPRETATIONS:** Individuals with aMCI with low Aβ1-42 in the ADNI dataset appear to have more advanced disease than those with high Aβ1-42. Selection criteria based on ADNI, as well as design of future studies, must account for potential confounds between biomarker status and disease severity to ensure that the former, and not the latter, is the true determinant of predictive accuracy.